December 12, 2003

Edwin L. Mongan, III
Manager, Environmental Stewardship
E.I. du Pont de Nemours & Company, Inc.
1007 Market Street
DuPont 6082
Wilmington, DE 19898

Dear Dr. Mongan:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Fluorobenzene posted on the ChemRTK HPV Challenge Program Web site on August 11, 2003. I commend E.I. du Pont de Nemours & Company, Inc. for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that DuPont advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Fluorobenzene

Summary of EPA Comments

The sponsor, E.I. du Pont de Nemours & Company, Inc., submitted a test plan and robust summaries to EPA for fluorobenzene (CAS No. 462-06-6) dated June 25, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 11, 2003. The sponsored chemical is fluorobenzene; some information was also included for the proposed analog chlorobenzene.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

2. Environmental Fate. The submitter needs to provide measured biodegradation data.

3. Health Effects. The submitter needs to provide additional information to satisfy the requirements for the classification of fluorobenzene as a "closed system intermediate" and qualify for reduced health effects testing.

4. Ecological Effects. The endpoint for invertebrates is addressed adequately using the data from analogs and SAR. However, ecological data submitted for fish are inadequate and EPA reserves judgement on the adequacy of submitted algae study on chlorobenzene (analog), pending submission of missing critical data elements.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Fluorobenzene Challenge Submission

GENERAL

For boh health and ecological effects the submitter needs to provide a justification for the analogs used. For health, the submitter needs to provide a comparison of the physicochemical characteristics, metabolism and available mammalian toxicity data for fluorobenzene and the proposed analog chlorobenzene.

Test Plan

Physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation and fugacity are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submitter indicates in its overall summary that "A hydrolysis test using OECD Guideline 111 is recommended to confirm this prediction (resistance to hydrolysis)." EPA assumes that the submitter will provide hydrolysis data following OECD TG 111 in order to satisfy this endpoint.

Biodegradation. The submitter provided estimated biodegradation data using BIOWIN v.400. Estimated biodegradation data are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured ready biodegradation data following OECD TG 301.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available for acute toxicity, repeated-dose toxicity, and gene mutation endpoints. Information provided for the micronucleus assay is insufficient and the submitter needs to provide additional information. EPA agrees that chlorobenzene appears to be a good analog for addressing developmental toxicity, however, the submitter needs to provide justification using robust summaries for the comparison of metabolism data, repeated-dose studies, and the physicochemical characteristics of the two chemicals.

Chromosomal aberrations. The study may be adequate but the robust summary is inadequate. The secondary source should be located and summarized or the additional information which was not utilized should be included.

The submitter requests an exemption from reproductive toxicity testing based on its claim that fluorobenzene is a "closed-system intermediate."

The Guidance for Testing Closed System Intermediates for the Challenge Program http://www.epa.gov/chemrtk/guidocs.htm allows for a reduced testing protocol provided certain criteria are met. The information required to judge a "closed-system intermediate" claim must address the following:

I. Site information
    A. Number of sites.
    B. Basis for "closed process" conclusion at each site.
        1) Process description.
        2) Monitoring data showing no detection.
        3) In the absence of monitoring data, the basis for believing that releases do not occur.
    C. Data on "presence in distributed products."
II. Information on transport (mode, volume, controls, etc)
III. A data search showing that the chemical is not present in other end products.

EPA believes that the information provided by the submitter is not adequate to satisfy the requirements for classification as a "closed system intermediate" and is not eligible for reduced testing in the HPV Challenge Program. The following information is needed to support this claim:

I.A. *Number of sites*: The submitter needs to identify all sites in the United States handling fluorobenzene and provide assurance that the chemical is managed in a closed system at all locations including sites that may not be controlled by the submitter. Only one contract site using imported fluorobenzene is described in the submission, however, information from the 1998 Inventory Update Rule indicates that fluorobenzene was imported by one company and manufactured by a second company. Assurance that the chemical is managed in closed systems at the U.S. manufacturing site and all alternate sites is needed.

IB. *Basis for closed process conclusion at each site*: The submitter needs to clarify if the imported chemical is received from overseas in an isotank ready for transport or whether the chemical is transferred at the port of entry into isotanks using closed pumps and piping. There is no discussion of handling of the chemical at alternate sites.

II. *If transport occurs, information on the mode of transport, volume, type of consignment, and controls during transport and transfer at dispatching and receiving sites*: The submitter needs to provide details about the isotanks that are delivered to a contract processing site and whether the chemical is imported in isotanks or whether a transfer to isotanks occurs at the port-of-entry. If a transfer occurs, then a description of the process is needed. The submitter needs to provide assurances concerning the handling practices of other possible manufacturers and importers.

I.C. *Data on presence in distributed product or the basis for believing it is not present*: The test plan states that the chemical is consumed at the end of processing, however it does not contain any information on the presence or absence of the chemical in distributed products.

III. Supporting evidence that the chemical is not present in other end-products. No additional supporting evidence is provided to substantiate that the chemical is not present in other end-products.

Unless additional information is provided to support the "closed system intermediate" claim, the following needs to be addressed:

Developmental and reproductive effects. Within the context of the reduced plan, the developmental data for the analog chlorobenzene are adequate if the analog is justified with additional information. However, if the "closed system intermediate" claim cannot be supported, then EPA recommends a combined protocol for developmental and reproductive effects (OECD 421) as an alternative testing approach. The combined protocol would address reproductive toxicity and provide specific information on fluorobenzene and developmental effects, since statistically significant effects were reported in the chlorobenzene studies.

Ecological Effects (fish, invertebrates, and algae).

Fish. For acute toxicity to fish, the studies submitted on fluorobenzene or chlorobenzene are inadequate. The studies were not performed in a closed system or with suitable monitoring of test substance concentrations and the chemical's loss during the test was not accounted for in both tests. No analytical measurement was performed in the fluorobenzene test. For the testing of chlorobenzene, the analytical measurements of test concentration in the vessels indicated only 0.26-2.2% of test material was recovered. In order to report the toxicity in nominal concentration, the recovery rate should have been at least 80%.

Invertebrates. The endpoint for invertebrates is addressed adequately using the data from analogs and SAR. The sponsor needs to provide some missing data elements in the robust summary.

Algae. EPA reserves judgement on the adequacy of submitted algae study on chlorobenzene (analog) pending submission of missing critical data elements. For the validity of the test, the cell concentration in the control cultures should have increased by the factor of at least 16 within three days.

Specific Comments on the Robust Summaries

Health Effects

Acute Toxicity. Information from Eitington, A.I. and I.P. Ulanova, 1975, should not be used in the test plan and robust summaries since the studies are considered unreliable.

Repeated-Dose Toxicity. A robust summary for a 28-day inhalation assay in rats lacked details and did not include the specific hematological, clinical chemistry and urinalysis parameters assessed, and the identity of the organs weighed and evaluated for histopathology.

Genetic Toxicity: mutations. The submitter should delete the sentence that states that fluorobenzene is not mutagenic in the Ames assay. Both studies are adequate and the issue of a positive response with hamster S9 in one study is not invalidated by the other study which relied on rat S9 only.

Genetic Toxicity: chromosomal aberrations: A robust summary for a negative micronucleus assay in mice did not provide sufficient information to evaluate the study. The severely deficient summary is mischaracterized for reliability as 'medium' when 'not assignable' is more appropriate.

Developmental Toxicity. A robust summary for a developmental toxicity study in rats exposed by inhalation to the analog chlorobenzene needs to include information on the magnitude of the reduction in body weight gain in high-concentration dams and GLP status.

Ecological Effects

Invertebrates. Missing study details noted in the summary for the studies of fluorobenzene and analogs (1-chloro-2-fluorobenzene, 1-chloro-3-fluorobenzene, and 1-chloro-4-fluoro-benzene) in *Daphnia magna* included the test system (i.e., static or renewal), test concentrations, number of daphnia per concentration (fluorobenzene), loading, endpoint that was evaluated (e.g., immobility), number of deaths and/or proportion of animals that displayed the signs of toxicity per concentration, and the test conditions (e.g., temperature and dissolved oxygen).

Algae. Missing study details noted in the summary for the study of chlorobenzene in *Selenastrum capricornutum* included test substance purity, number of replicates per concentration, use and response of control cultures, statistical methods, lighting, pH and cell concentrations per test concentration at each measurement interval, and 95% confidence limits.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.